REMARKS

Favorable reconsideration is respectfully requested in view of the foregoing amendments and following remarks.

Applicants confirm with thanks the Examiner's indication during the telephone conference held on August 18, 2008 that the finality of the last Office Action is withdrawn.

Applicants wish to express their sincere appreciation of the Examiner Charlesworth Rae and his supervisor, Supervisory Examiner Sharmila Landau, for their courtesy and assistance provided during the personal interview held on August 21, 2008.

Claims 1 and 10 have been amended as discussed during the interview. Specifically, claims 1 and 10 have been amended to clarify that the water-soluble metal chloride is contained in the aqueous solution in a light-stabilizing effective amount. Claims 1 and 10 have also been amended to clarify that the aqueous liquid preparation comprises the claimed ingredients in an aqueous solution. Claim 11 is cancelled without prejudice to expedite allowance.

Claims 1-10 solely rejected under 35 USC 103(a) as unpatentable over Koida et al. in view of Kita et al. and Remington's. This ground of rejection is respectfully traversed as applied to the amended claims.

As discussed during the interview, the combined teachings of the cited references fail to render obvious the claimed invention as amended. The cited Koida teaches the claimed compound but does not teach the compound in combination with any water-soluble metal chloride. The compound is only combined with mannitol, sucrose, lactose and polyethylene glycol.

Similarly, Kita teaches the claimed compound but does not teach the compound in combination with any water-soluble metal chloride.

Remington's teaches a long list of isotonicity agents which can be used to adjust the isotonicity of eye and nasal drops. Remington fails to disclose any of these agents in combination with the claimed compound. The inventors have surprisingly discovered that a small group of these isotonicity agents, namely the water-soluble metal chlorides, unexpectedly stabilize the claimed compound from light. The Examiners appeared to be persuaded by these facts during the interview.

During the interview, the Declaration of record was reviewed to determine if the comparative experiments were satisfactory to the Examiners for showing unexpected results for

the claims. The Examiners appeared satisfied that the experiments support the unexpected light stability of the claimed compound by the claimed group of water soluble metal chlorides, based upon the results of Experiment 1 of sodium chloride, potassium chloride and calcium chloride.

Experiment 2 of the Declaration compares the light stabilizing effect of sodium chloride to the combination of glycerin and boric acid. Experiment 4 compares the light stabilizing effect of sodium chloride to glycerin. The experiment also discusses replacing glycerin with glucose or mannitol in Formulation 16, however the Table 4 does not reflect this fact.

However the Examiners suggested a side-by-side comparison of the claimed invention with the closest prior art. The closest prior art is Koida. Koida teaches combining the claimed compound with mannitol, sucrose, lactose or polyethylene glycol. The Examiners recommended that a Supplemental Declaration be filed comparing the light stabilizing activity of a claimed water soluble metal chloride with any one of mannitol, sucrose, lactose or polyethylene glycol.

Submitted herewith is a Supplemental Declaration to establish the unobviousness of the present invention from Koida et al., by clarifying the description of Experiment 4 in the earlier Declaration, which was pointed out to be indefinite by the Examiner during the interview.

Koida et al. disclose a method of preventing racemization of bepotastine, which includes addition of sugars to an oral solid preparation. As reported in the Declaration, Formulation 7 (containing 0.6% w/v% sodium chloride) remained pale-yellow and clear even after exposure to light, but Formulation 18 (containing 3.3 w/v% glucose) and Formulation 19 (containing 3.3 w/v% mannitol) both turned black green.

It has thus been clearly established that the bepotastine-stabilizing effect achieved by the addition of water-soluble metal chloride to an aqueous solution containing bepotastine cannot be achieved by the addition of sugars. As mentioned above, stabilization of bepotastine by the addition of sugars is different from stabilization of bepotastine by the addition of water-soluble metal chloride, and those of ordinary skill in the art cannot easily conceive stabilization of bepotastine achieved by the present invention by the addition of water-soluble metal chloride, from the technique of Koida et al.

In summary, it is respectfully submitted that the prior art fails to suggest the unexpected light stabilization of the claimed compound using a water-soluble metal chloride.

In view of the foregoing, it is believed that each ground of rejection set forth in the Official Action has been overcome, and that the application is now in condition for allowance. Accordingly, such allowance is solicited.

Respectfully submitted,

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of

Masayo HIGASHIYAMA : Docket No. 2004_1016A

Serial No. 10/500,354 : Group Art Unit 1611

Filed on June 30, 2004 : Examiner: Rae, Charlesworth E

For: AQUEOUS LIQUID PREPARATIONS AND LIGHT-STABILIZED AQUEOUS LIQUID PREPARATIONS

DECLARATION UNDER 37 CFR §1.132

Honorable Commissioner of
Patents,
P.O. Box 1450
Alexandria, Virginia 22313-1450

Sirs:

I, Masayo HIGASHIYAMA, citizen of Japan and residing in Suita-shi, Osaka, Japan, sincerely declare;

That my education and employment history is as follows:

1. I graduated from Nagoya City University, Japan, Graduate School of Pharmaceutical Sciences, in March 1995,
2. I received a Doctor's degree in Engineering from Kyushu Institute of Technology, Japan, in September 2007, and
3. since April 1995 up to this time, I have been an employee of Senju Pharmaceutical Co., Ltd., and engaged in the pharmaceutical research of ophthalmic formulation;

That I am a member of the Pharmaceutical Society of Japan since November 1993, and the Controlled Release Society since January 2002;

That I am a co-author of the following papers:

1. Yasueda S, Higashiyama M, Yamaguchi M, Isowaki A, Ohtori A; Corneal critical barrier against the penetration of dexamethasone and lomefloxacin hydrochloride: evaluation by the activation energy for drug partition and diffusion in cornea, *Drug Dev Ind Pharm.*, 2007, 33(8), 805-11,
2. Higashiyama M, Inada K, Ohtori A, Kakehi K; NMR

analysis of ion pair formation between timolol and sorbic acid in ophthalmic preparations, *J Pharm Biomed Anal.*, 2007, 43(4), 1335-42,

3. Higashiyama M, Tajika T, Inada K, Ohtori A; Improvement of the ocular bioavailability of carteolol by ion pair, *J Ocul Pharmacol Ther.*, 2006, 22(5), 333-9,

4. Yasueda S, Higashiyama M, Shirasaki Y, Inada K, Ohtori A; An HPLC method to evaluate purity of a steroidal drug, loteprednol etabonate, *J Pharm Biomed Anal.*, 2004, 36(2), 309-16, and

5. Higashiyama M, Inada K, Ohtori A, Tojo K; Improvement of the ocular bioavailability of timolol by sorbic acid, *Int J Pharm.*, 2004, 272(1-2), 91-8;

That I am the sole inventor of the above-identified U.S. patent application SN 10/500,354; and

That I conducted the following experiment to demonstrate the unexpected superior effect of the present invention that (+)-(S)-4-[4-[(4-chlorophenyl)(2-pyridyl)methoxy]piperidino]butyric acid and a pharmacologically acceptable acid addition salt thereof, particularly bepotastine besilate, can be light-stabilized in water by adding water-soluble metal chloride, the results of which follow hereunder.

Experiment

Effect of water-soluble metal chloride on light-stability of bepotastine besilate in aqueous solution as compared to the effect of glucose or mannitol

Test method

The aqueous liquid preparations (Formulations 7, 18 and 19) shown in the following Table 1, which contained bepotastine besilate, were prepared according to conventional methods and filled in glass ampoules by 5 mL each. Using the Xenon long-life fade meter (FAL-25AX-Ec manufactured by SUGA TEST INSTRUMENTS Co., Ltd.), a light corresponding to not less than 200 $W \cdot h/m^2$ in a total near-ultraviolet radiation energy was irradiated

(irradiation time: 23-34 hr), and the appearance of each formulated liquid preparation was observed. The amount of light exposure was measured by a quinine chemical actinometry system described in the Drug Approval and Licensing Procedures in Japan 2001.

Table 1

Formulation	7	18	19
bepotastine besilate	1.5 g	1.5 g	1.5 g
sodium dihydrogen phosphate dihydrate	0.1 g	0.1 g	0.1 g
sodium chloride	0.6 g	-	-
glucose	-	3.3 g	-
mannitol	-	-	3.3 g
benzalkonium chloride	0.005 g	0.005 g	0.005 g
sodium hydroxide	suitable amount	suitable amount	suitable amount
total amount	100 mL	100 mL	100 mL
pH	6.8	6.8	6.8
appearance after light irradiation	pale-yellow and clear	black green, containing precipitate	black green, containing precipitate

Test results

The appearance after light irradiation did not change from that immediately after preparation and was pale yellow and clear for Formulation 7, comprising 0.6 w/v% sodium chloride. Meanwhile, the appearance after light irradiation turned black green for Formulation 18 and Formulation 19, comprising 3.3 w/v% glucose and 3.3 w/v% mannitol, and a precipitate was observed. The results indicate that a water-soluble metal chloride in a light stabilizing effective amount improves light-stability of bepotastine besilate, and saccharides such as glucose and mannitol do not improve light-stability of bepotastine besilate.

I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false

statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Signed at Osaka Japan on this 22 day of December, 2008

Masayo Higashiyama

Masayo HIGASHIYAMA